2020-11-30

EuReCa International PhD Program

PhD thesis project

2021 Call for application

Mechanotransduction at the Golgi apparatus

General information

Call	2021
Reference	2021-09-MANNEVILLE_MISEREY-LENKEI
Keyword(s)	Tension; Cytoskeleton; RhoGTPases; Intracellular trafficking; Cancer

Director(s) and team

Thesis director(s)	Jean-Baptiste Manneville & Stéphanie Miserey-Lenkei
Research team	Molecular Mechanisms of Intracellular Transport
Research department	UMR144-Cell Biology and Cancer

Description of the PhD thesis project

Research focus of the lab:

Our lab is broadly interested in membrane trafficking and in its perturbations associated with human pathologies such as cancer. We are elucidating the various biological and biophysical mechanisms of the regulation of vesicular transport and membrane trafficking, using a combination of approaches, including live cell imaging, micro-patterning and microfabrication, reconstitution of transport events using model membranes and intracellular microrheology with optical tweezers.

The lab is headed by Bruno Goud who is a world leader in the field of RAB GTPases.

The thesis will be co-supervised by Jean-Baptiste Manneville (biophysicist) and Stéphanie Miserey-Lenkei (cell biologist).

Abstract of the PhD project:

Cells can sense and respond to external forces and mechanotransduction events appear to be critical for most cellular functions. While mechanotransduction has been extensively studied at the plasma membrane and at the nucleus, the impact of forces on other organelles is still not clear.

Our PhD project will study mechanotransduction at the Golgi apparatus (GA), a central organelle for intracellular transport pathways.
We will ask three questions:

1) Can external and internal forces propagate to the GA and impact its tension?
2) Is the tension of the GA regulated by actin dynamics and/or the composition of Golgi membranes and the Golgi matrix?
3) Do post-Golgi trafficking and polarized secretion depend on the tension of the GA?

To achieve these goals, we will develop new fluorescent probes to visualize and quantify tension at the GA. The probes will be first tested in the mammalian RPE-1 cell line then used in the context of pancreatic ductal adenocarcinoma (PDAC).

Our results should provide new fundamental insights in the role played by mechanical tension in force transduction at the level of the GA as well as a better understanding of the physical mechanisms underlying polarized secretion during metastatic niche formation in PDAC.

International, interdisciplinary & intersectoral aspects of the project

International
The project will be developed in collaboration with Laura Machesky (Beatson Institute, Glasgow, UK) expert in PDAC metastatic niche formation, Sirio Dupont (U. Padova, Italy) expert in YAP/TAZ signalling, and Aurélien Roux (U. Geneva, Switzerland) for the development of Flipper tension probe specific to the GA.

Intersectoral
We will collaborate with Aurélien Roux's industrial partner Spirochrome together with the chemistry group of Stefan Matile (U. Geneva) to develop a Golgi tension probe.

Interdisciplinary
The project mixes physico-chemical approaches and tools (optical tweezers, microfluidics, force measurements, synthesis of novel fluorescent tension sensors) with fundamental cell biology questions related to mechanotransduction and to metastatic niche formation.

Recent publications

1) The Golgi apparatus and cell polarity: Roles of the cytoskeleton, the Golgi matrix, and Golgi membranes. Ravichandran Y, Goud B, **Manneville JB**. Curr Opin Cell Biol. 2020 Feb; 62:104-113. doi: 10.1016/j.ceb.2019.10.003.

2) Role of a Kinesin Motor in Cancer Cell Mechanics. Mandal K, Pogoda K, Nandi S, Mathieu S, Kasri A, Klein E, Radvanyi F, Goud B, Janmey PA, **Manneville JB**. Nano Lett. 2019 Nov 13; 19(11):7691-7702. doi: 10.1021/acs.nanolett.9b02592.

3) Extracellular matrix mechanical cues regulate lipid metabolism through Lipin-1 and SREBP. Romani P, Brian I, Santinon G, Pocaterra A, Audano M, Pedretti S, Mathieu S, Forcato M, Bicciato S, **Manneville JB**, Mitro N, Dupont S. Nat Cell Biol. 2019 Mar;21(3):338-347. doi: 10.1038/s41556-018-0270-5

4) RAB6 and microtubules restrict protein secretion to focal adhesions. Fourriere L, Kasri A, Gareil N, Bardin S, Bousquet H, Pereira D, Perez F, Goud B, Boncompain G, **Miserey-Lenkei S**. J Cell Biol. 2019 Jul 1;218(7):2215-2231.

5) Coupling fission and exit of RAB6 vesicles at Golgi hotspots through kinesin-myosin interactions. **Miserey-Lenkei S**, Bousquet H, Pylypenko O, Bardin S, Dimitrov A, Bressanelli G, Bonifay R, Fraisier V, Guillou C, Bougeret C, Houdusse A, Echard A, Goud B. Nat Commun. 2017 Nov 1;8(1):1254. doi: 10.1038/s41467-017-01266-0.

Expected profile of the candidate

We are looking for a highly motivated applicant with a strong desire to explore challenging biophysical aspects of cell biology and a solid capacity for independent and creative thinking.

Background in cell biology, mechanobiology and membrane trafficking is strongly recommended. Background in biophysics and optics is a plus but not compulsory. Previous training in cell culture, biochemistry, molecular cell biology, live cell imaging techniques and physical tools such as micromanipulation with optical tweezers or microfabrication would be ideal.

The applicant should be fluent in English.